



MMHCC Newsletter February 2006

MouseLine

Mice Show What Happens Before Tumors Spread

A recent study in mice reported that normal cells from bone marrow may play an important role in the spread of cancer and that blocking these cells could potentially prevent some tumors from invading new tissues (metastasizing).

By tracking the spread of tumors from the skin to the lungs of mice, researchers found that before cancer cells reached the lungs, bone marrow cells had migrated there first and modified the environment for their arrival.

Specifically, the bone marrow cells had created clusters, or niches, where circulating tumor cells could "dock" and grow. Nearly every new tumor that appeared in the lungs originated in one of the niches, the researchers reported in the December 8 *Nature*.

"Tumors recruit these bone marrow cells and use them to establish new tumors," says Dr. Shahin Rafii of Weill Medical College of Cornell University, who co-led the research.

In what Dr. Patricia Steeg of NCI's Center for Cancer Research (CCR), who wrote an accompanying commentary, called an ingenious experiment, the researchers showed how tumor cells and bone marrow cells migrated through the mice by tagging them with fluorescent proteins that could be seen through the microscope.

As a first step, the researchers eradicated the mouse bone marrow cells and replaced them with bone marrow cells that had been tagged green. Once these were established, the mice received skin injections of cancer cells - tagged red - that were expected to travel to the lungs.

The first cells to reach the lungs were the green bone marrow cells, 12 to 14 days after the injections. The red cancer cells appeared 18 days after the injections, and by day 23, small metastases had formed. Ninety-five percent of the tumors appeared at the precise locations where bone marrow cells had created niches.

The researchers then discovered that inhibiting the bone marrow cells could prevent metastases from forming in the mice.

Most cancer deaths occur because primary tumors invade new tissues, a process that involves cancer cells breaking off from tumors and traveling through the bloodstream to establish tumors elsewhere. If the new findings are confirmed in mice and extended to humans, then researchers might have unforeseen opportunities to intervene.

"This research opens the door to all of the early events in metastasis that we did not know about before," says study co-leader Dr. David Lyden, also of Cornell University. His laboratory will now search for the molecules that tumors presumably release into the bloodstream to mobilize bone marrow cells to go to particular regions.

Meanwhile, Dr. Rafii will try to understand how the bone marrow cells, which express a protein called vascular endothelial growth factor receptor 1 (VEGFR1), emerge from pockets deep within bone marrow. Preventing their emergence could prevent some metastases, he notes.

Cells that express VEGFR1 have been linked to the formation of blood vessels that supply tumors with nutrients, and in this study, the researchers report that the cells may also help cancer cells adhere to niches and develop into tumors.





MouseLine cont.

The researchers also report finding clusters of cells expressing VEGFR1 in some human primary tumors and metastatic tissues.

Inhibiting VEGFR1 or other factors involved in the formation of human tumors would "be of great interest for potentially blocking metastasis," especially in cancer patients who are at high risk, said Dr. Steeg in her commentary.

The novelty of the study is the idea that before tumors arrive at their new destinations, nonmalignant cells play a major role in preparing the sites for them, says Dr. Lyden.

This idea raises many questions. For instance, might the risk of metastasis depend on how well a person mobilizes bone marrow cells? If so, this ability might be in part genetic, says Dr. Rafii, noting that some mouse strains are better at this than others.

Another question is whether chemotherapy used to prevent metastasis might be effective in some patients by preventing niches from forming. "Nobody knows how chemotherapy works," Dr. Rafii says. "We think it targets tumors, but it may be targeting the niches."

By Edward R. Winstead

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Meetings

March 1 - 5, 2006

AACR Special Conference - Cancer Susceptibility and Cancer Susceptibility Syndromes

Maui, Hawaii

Co-chairs: Pier Paolo Pandolfi and Alan D'Andrea

Meeting information: <http://www.aacr.org/page5188.aspx>

March 15 - 19, 2006

PTEN Pathways

Cold Spring Harbor, NY

Meeting Information: <http://meetings.cshl.edu/meetings/pten06.shtml>

April 1 – 5, 2006

AACR Annual Conference

Washington, D.C.

Meeting information: <http://www.aacr.org/page5573.aspx>

Please visit the MMHCC at the NCI booth (Exhibit #901)

May 18 - 19, 2006

The Laboratory Mouse in Translational Cancer Research and Discovery

New York City, NY

Meeting information: <http://www.jax.org/courses/events/coursedetails.do?id=339>





Notices and Funding Opportunities

NCI Funding Policy Available Online

Information about NCI's official funding policy for FY 2006 Research Project Grants (RPGs) is available online at <http://deainfo.nci.nih.gov/grantspolicies/FinalFundLtr.htm>

Information about the major RPG funding mechanisms for competing and noncompeting awards is included. Information about funding policies for other institutes can be found online at <http://grants.nih.gov/grants/financial/index.htm>

Request for Information (RFI): Nomination of Knockout Mice for Deposition in Public Repositories

NOT-DA-06-008

Multiple Institutes

<http://grants.nih.gov/grants/guide/notice-files/NOT-DA-06-008.html>

March IACUC 101 and PRIMR/ARENA Annual IACUC Meeting in Boston

NOT-OD-06-027

National Institutes of Health

<http://grants.nih.gov/grants/guide/notice-files/NOT-OD-06-027.html>

April IACUC 101 and 201 Workshops in Richmond, Virginia

NOT-OD-06-034

National Institutes of Health

<http://grants.nih.gov/grants/guide/notice-files/NOT-OD-06-034.html>

Innovative Technologies for Molecular Analysis of Cancer

RFA-CA-07-006, RFA-CA-07-007

National Cancer Institute

<http://grants.nih.gov/grants/guide/rfa-files/RFA-CA-07-006.html>

<http://grants.nih.gov/grants/guide/rfa-files/RFA-CA-07-007.html>

Application of Emerging Technologies for Cancer Research

RFA-CA-07-008, RFA-CA-07-009

National Cancer Institute

<http://grants.nih.gov/grants/guide/rfa-files/RFA-CA-07-008.html>

<http://grants.nih.gov/grants/guide/rfa-files/RFA-CA-07-009.html>





Notices and Funding Opportunities cont.

Innovations in Cancer Sample Preparation

RFA-CA-07-010, RFA-CA-07-011

National Cancer Institute

<http://grants.nih.gov/grants/guide/rfa-files/RFA-CA-07-010.html>

<http://grants.nih.gov/grants/guide/rfa-files/RFA-CA-07-011.html>

Disease Investigation through Specialized Clinically-Oriented Ventures in Environmental Research

RFA-ES-06-001

National Institute of Environmental Health Sciences

<http://grants.nih.gov/grants/guide/rfa-files/RFA-ES-06-001.html>

Tumor Microenvironment Network (TMEN)

RFA-CA-06-014

National Cancer Institute

<http://grants.nih.gov/grants/guide/rfa-files/RFA-CA-06-014.html>

Repository News

The MMHCC Mouse Repository is an NCI-supported resource for the distribution of mouse cancer models and associated strains. The Repository makes strains available to all members of the scientific community. Up to 3 breeder pairs of each available strain may be ordered.

Newly accepted strains

The following strains have recently been accepted into the MMHCC Repository and are available for distribution (*please click on the specific link, below, for additional information*):

1. B6.Cg-Tg(LPV-TAg1135)11Tvd
http://mouse.ncicrf.gov/available_details.asp?ID=01XM5
2. 129S4- *Trp53*^{tm2Tyj}
http://mouse.ncicrf.gov/available_details.asp?ID=01XM2
3. 129S4- *Trp53*^{tm2.1Tyj}
http://mouse.ncicrf.gov/available_details.asp?ID=01XL9
4. 129S4- *Trp53*^{tm3Tyj}
http://mouse.ncicrf.gov/available_details.asp?ID=01XM3
5. 129S4- *Trp53*^{tm3.1Tyj}
http://mouse.ncicrf.gov/available_details.asp?ID=01XM1

More information can be found on the Mouse Repository's website: <http://mouse.ncicrf.gov>





Repository News – Last Call



The following strains will be maintained as live colonies until the end of **April 2006**. After this date, they will be supplied as cryopreserved embryos. If you foresee using one of these strains in the near future, order now! Please be aware that all necessary paperwork (order form, MTA, etc.) needs to be completed and received by the Repository before the end of April 2006 in order to receive live mice.

1. STOCK *Tgfb1*^{tm1Doe} *Rag2*^{tm1Fwa}
http://mouse.ncicrf.gov/available_details.asp?ID=01XA6
2. STOCK Tg(NES-TVA)J12Ech
http://mouse.ncicrf.gov/available_details.asp?ID=01XH4
3. FVB-Tg(KRT14-E6)5737Plam
http://mouse.ncicrf.gov/available_details.asp?ID=01XJ8
4. B6;129-*E2f4*^{tm1Lees}
http://mouse.ncicrf.gov/available_details.asp?ID=01XK7
5. B6D2F2-Tg(ARR2/Pbsn-FGF8)3Prb
http://mouse.ncicrf.gov/available_details.asp?ID=01XL4

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